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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,355	GIESELER ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *7,8,13,20-24,40,55,60-65,67-71,73 and 75-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,9,10,15,16,26-28,37-39,41-44,50,52,53,56-59 and 81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *June 12, 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,6-10,13,15,16,20-24,26-28,37-44,50,52,53,55-65,67-71,73 and 75-81.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 1,2,6-10,13,15,16,20-24,26-28,37-44,50,52,53,55-65,67-71,73 and 75-81.

Detailed Action

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on November 13, 2009 is acknowledged.

Applicant has elected the invention of Group I, claim(s) 1-2, 6-10, 13, 20-24, 26-28, 37-44, 50, 52-53, 55-59, 75-79 and 81, drawn to a method of delivering an active agent to a reservoir cell of a mammal, the method comprising administering to the mammalian subject a lipid-active agent complex comprising the active agent and at least one targeting ligand, wherein the reservoir cell is infected with, or susceptible to infection with, an infectious agent.

Within Group I, Applicant has elected the following species, wherein:

i) the active agent is a lectin;

ii) the targeting ligand is fucose;

iii) the infectious agent is a virus; and

iv) the reservoir cell recited is dendritic cell.

1. **Restriction is required under 35 U.S.C. 121 and 372.**

Upon further review of the claims, the Examiner sets forth the following amendment to the Requirement for Restriction. This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, Applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-2, 6-10, 13, 20-24, 26-28, 37-44, 50, 52-53, 55-59, 76-79 and 81, drawn to a method of delivering an active agent to a reservoir cell of a mammal, the method comprising administering to the mammalian subject a lipid-active agent complex comprising the active agent and at least one targeting ligand, wherein the reservoir cell is infected with, or susceptible to infection with, an infectious agent.

Group II, claim(s) 60-65, 67-71, 73 and 80, drawn to a targeting system for delivery of an active agent to a reservoir cell, the system comprising a lipid-active agent complex and a targeting ligand on the outer surface of the lipid-active agent complex.

Group III, claim(s) 75, drawn to a method for preferentially delivering an active agent to a cell with a chronic non-infectious disease, the method comprising administering a lipid-active agent complex comprising the active agent and at least one targeting ligand.

2. **The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1** because, under PCT Rule 13.2, they lack the same or corresponding special technical feature for the following reasons:

A 371 case is considered to have unity of invention only when there is a technical relationship among those inventions involving one or more of the same or corresponding technical features. The expression "special technical feature' means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. In the instant application, WO 98/07408 (*of record in IDS) discloses a method of delivering an active agent to a reservoir cell of a mammal, the method comprising administering to the mammalian subject a liposome composition comprising DOTAP and at least one cholesterol or cholesterol derivative, a biologically active agent, i.e. nucleic acid DNA, and a targeting ligand. Thus, Claim 1 does not contribute over the prior art.

Inventions I and III are directed to related processes. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are drawn to targeting different cell populations, i.e. a reservoir cell (Invention I) versus a non-reservoir cell (Invention III) having different disease states, wherein those of ordinary skill in the art would immediately recognize a dendritic cell infected with HIV, for example, is distinctly different than a hepatic cell suffering from non-alcoholic fatty liver disease. Furthermore, the inventions as claimed do

not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Inventions I and III and Invention II are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the Inventions I and III methods may be practiced with structurally distinct delivery systems comprising distinctly different active agents, e.g. a gene-silencing RNA molecule, a protein-coding DNA molecule, or an apoptosis inhibitor, as evidenced by the claims.

The Examiner has required restriction between product and process claims. Where Applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder. Further, note that the prohibition against double patenting

rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the Examiner before the patent issues. See MPEP § 804.01.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, Applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, Applicant must indicate which of these claims are readable upon the elected invention.

Should Applicant traverse on the ground that the inventions are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Election of Applicant's invention(s) was made with traverse. Applicant argues that the proposed different groups do not possess sufficient differences to warrant issuancy of separate patents.

Applicant's argument(s) has been fully considered, but is not persuasive. Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (M.P.E.P. §818).

Claims 7-8, 13, 20-24, 40, 55, 60-65, 67-71, 73, 75-80 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-2, 6, 9-10, 15-16, 26-28, 37-39, 41-44, 50, 52-53, 56-59 and 81 are under consideration.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on June 12, 2008 that have been considered.

The information disclosure statement filed June 12, 2008 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because: i) the Charan et al reference has been lined through because the copy provided by Applicant is illegible (A copy of the first page is provided in the Appendix of this Office Action, for example.); and ii) Each publication (specifically, Charan et al) must be identified by publisher, author (if any), title, relevant pages of the publication, and date and place of publication. The **date of publication** supplied must

include at least the month and year of publication, except that the year of publication (without the month) will be accepted if the Applicant points out in the information disclosure statement that the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue. The place of publication refers to the name of the journal, magazine, or other publication in which the information being submitted was published.

The signed and initialed PTO Forms 1449 are mailed with this action.

Oath/Declaration

3. **The oath or declaration is defective**. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the papers filed April 23, 2007 are photocopies that are essentially illegible.

Specification

4. **The disclosure is objected to** because it contains an embedded hyperlink and/or other form of browser-executable code. See pg 45, line 2; pg 74, line 7; and pg 82, line 24. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

5. **Claims 50 and 53 are objected to because of the following informalities**:

These claims each identify Con-A and/or MHL as lectins that may be used in the claimed invention. However, the claims do not first identify the lectin by its complete name prior to using its acronym. The abbreviation should be spelled out in the first appearance of the claims and should be followed by the abbreviation in parentheses, e.g. Epidermal Growth Factor (EGF).

Appropriate correction is required.

6. **Claim 81 is objected to because of the following informalities**:

These claims each identify CRD as a receptor to which the targeting ligand is required to bind. However, the claims do not first identify the CRD receptor by its complete name prior to using its acronym. The abbreviation should be spelled out in the first appearance of the claims and should be followed by the abbreviation in parentheses, e.g. Epidermal Growth Factor (EGF).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

7. **Claim 58 is rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The claim is indefinite because i) the phrase "a lipid" may refer to the entire lipid component or a specific lipid component , ii) the specific lipid component to which the ratio is to be compared is undisclosed, wherein the specification discloses a multitude of lipids that may be present in te lipid-active agent complex (pg 40, 94), and iii) the unit value, e.g. molecular weight or molar %, by which the ratio of the lipid versus active agent is undisclosed.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the Applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Applicant for patent or (2) a patent granted on an application for

patent by another filed in the United States before the invention by the Applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. **Claims 1-2, 6, 9, 15-16, 26-28 and 37-39 are rejected under 35 U.S.C. 102(e)** as being anticipated by Hartmann et al (U.S. Patent 6,949,520).

Hartmann et al disclose a method of delivering an active agent to a reservoir cell of a mammal, the method comprising administering to the mammalian subject a lipid-active agent complex, i.e. a liposome, comprising a targeting ligand (col. 25, lines 44-46), and may further comprise additional active agents (col. 26, lines 48-55) and/or accessory factors, e.g. formulated with pharmaceutically acceptable salts (col. 28, lines 52-67).

The subject may have a viral infection, e.g. HIV (col. 6, lines 52-64, col. 22).

The target cell is an interferon-producing cell, i.e. a dendritic cell (col.'s 1-2), contacted in vivo (col. 8, lines 50-55).

To the extent that the intended use of the active agent is to treat a subject suffering from an infectious agent, i.e. a virus, absent evidence to the contrary, the infectious agent is reasonably considered to "be susceptible" to the biological effects of the active agent.

The lipid-active agent complex may be administered via any art-recognized means, e.g. parenteral, transdermal, intravenous, infusion, bolus injection, etc…, to delivery the active agent to the desired site (col. 26, lines 58-64; col. 31, lines 16-17), wherein local injection includes the blood vessel supplying a target tissue, e.g. hepatic artery (col. 8, lines 16-19; col. 32, line 54-col. 33, line 7).

9. **Claims 1-2, 6, 9, 15, 26, 28 and 81 are rejected under 35 U.S.C. 102(b)** as being anticipated by Smyth-Templeton et al (WO 98/07408; *of record in IDS).

Smyth-Templeton et al disclose a method of delivering an active agent to a reservoir cell of a mammal, the method comprising administering to the mammalian subject a lipid-active agent complex, i.e. liposome, composition comprising DOTAP and at least one cholesterol or cholesterol derivative, a biologically active agent, i.e. nucleic acid DNA, and a targeting ligand.

The liposomes may be administered via subcutaneous, intravenous, intramuscular, intraperitoneal, intradermal and intrauteral means (pgs 14-15, joining ¶). The lipid-active agent complex may be administered intrahepatically via tail-vein injection (pg 9, Figure 7).

Conditions to be treated include immunological and viral diseases (pg 14, ¶1).

The lipid-active agent complex may further comprise one or more additional active agents (pg 11, ¶2).

The targeting ligand may be for the hepatic asialoglycoprotein receptor (pg 34, ¶2), which comprises a carbohydrate recognition domain (CRD; specification, pg 63, lines 15-22; pg 64, lines 18-19).

Smyth-Templeton et al do not disclose specific target cells infected or susceptible to infection, with an infectious agent, e.g. a virus, rather targeted delivery to specific organs, e.g. brain, heart, lungs or liver (pg 18, last ¶). However, it is commonly recognized by those of ordinary skill in the art and the general public that cells of the brain, heart, lungs or liver are susceptible to viral infection, e.g. influenza (lung).

10. **Claims 1-2, 6, 9, 15-16, 26, 28, 38-39, 41-42 and 81 are rejected under 35 U.S.C. 102(a)** as being anticipated by Arigita et al (Infection and Immunity 71(9): 5210-5218, 2003).

Arigita et al teach a method of preferentially delivering an active agent to a reservoir cell, specifically a dendritic cell, of a mammalian subject, the method comprising administering to the mammalian subject (pg 5212, In vivo studies) a lipid-active agent complex comprising at least one targeting ligand on the outer surface of the complex.

The lipid-active agent complex is a liposome-active agent complex, wherein said active agent is encapsulated in said complex (pg 5211, Preparation).

The lipid-active agent complex comprises at least one accessory factor, i.e. the pH-modifying agent Tris (pg 5211, Materials).

Arigita et al do not teach the dendritic cells to be susceptible to infection with an infectious agent such as a virus. However, those of ordinary skill in the art have long-recognized dentritic cells are susceptible to infection with, e.g. HIV (specification, pg 90, lines 24-25).

The lipid-active agent complex is administered subcutaneously (pg 5212, In vivo studies).

The targeting ligand is mannose.

Arigita et al do not teach that the mannose targeting ligand is recognized by a C-type receptor and/or a non-C-type receptor expressing a C-type lectin-like carbohydrate recognition domain (CRD); however, such is considered an inherent property, absent evidence to the contrary (specification, pgs 11-12; pg 65, lines 1-5). "Products of identical chemical composition can not have mutual exclusive properties." A compound and its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present. *In re Spada*, 911 F.2d 705,709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP §2112.01. The burden is shifted to the Applicant to show that the mannose targeting ligand taught in the prior art does not inherently possess the same properties as the instantly claimed mannose targeting ligand.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. **Claims 1-2, 6, 9, 15-16, 26-28, 37-39, 41-44 and 81 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Hartmann et al (U.S. Patent 6,949,520) in view of Arigita et al (Infection and Immunity 71(9): 5210-5218, 2003) and Figdor et al (U.S. Patent 7,148,329).

Determining the scope and contents of the prior art.

The teachings of Hartmann et al are discussed above and incorporated herein.

Hartmann et al do not teach the targeting ligand to be recognized by a C-type lectin-like carbohydrate recognition domain (CRD). However, at the time of the invention, Arigita et al taught liposomes comprising mannose targeting ligands (as discussed above).

Neither Hartmann et al nor Arigita et teach the targeting ligand to be fucose. However, at the time of the invention, Figdor et al disclosed that fucose or mannose may be used to bind to C-type lectins on the surface of dendritic cells (Abstract).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and

have the practical experience in lipid-active agent complex formation. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a first targeting ligand as taught by Hartmann et al with a second targeting ligand, specifically fucose, capable of binding to C-type lectin-like carbohydrate recognition domains as taught by Figdor et al in view of Arigita et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)." When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute a first targeting ligand with a second targeting ligand, specifically fucose, capable of binding to C-type lectin-like carbohydrate recognition domains because Arigita et al successfully demonstrate the ability of mannose-labeled liposomes to be taken up by the targeted dendritic cells and Figdor et al disclose that both mannose and fucose targeting ligands are recognized by C-type lectins on the surface of dendritic cells.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

12. **Claims 10 and 52 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Hartmann et al (U.S. Patent 6,949,520) in view of Arigita et al (Infection and Immunity 71(9): 5210-5218, 2003) and Figdor et al (U.S. Patent 7,148,329), as applied to Claims 1-2, 6, 9, 15-16, 26-28, 37-39, 41-44 and 81 above, and in view of LaGrone (U.S. Patent 5,981,493).

Determining the scope and contents of the prior art.

Neither Hartmann et al, Arigita et al nor Figdor et al disclose/teach active agent encapsulated in the lipid-active agent complex to be a plant lectin. However, at the time of the invention, LaGrone disclose a method of delivering an active agent to a reservoir cell, i.e. HIV-infected reservoir cells, specifically mononuclear phagocytic lineage cells that eventually become dendritic cells (col. 4, lines 25-37, 52-58), comprising the administration of a plant lectin (col. 4, lines 8-24) encapsulated within a liposome (col. 10, line 9).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in lipid-active agent complex formation. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a first active agent as taught by Hartmann et al and/or Arigita et al with a second active agent, specifically a plant lectin as taught by LaGrone with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute a first active agent with a second active agent, specifically a plant lectin because LaGrone suggests that the use of plant lectins to selectively destroy HIV-infected reservoir cells to facilitate the eradication of HIV or severely curtail the progress of HIV infection in a patient in need of treatment.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

13. **Claims 58-59 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Hartmann et al (U.S. Patent 6,949,520) in view of Arigita et al (Infection and Immunity 71(9): 5210-5218, 2003), Figdor et al (U.S. Patent 7,148,329) and LaGrone (U.S. Patent 5,981,493), as applied to Claims 1-2, 6, 9-10, 15-16, 26-28, 37-39, 41-44, 52 and 81 above, and in view of Haas et al (U.S. 2005/0181038).

Determining the scope and contents of the prior art.

Neither Hartmann et al, Arigita et al, Figdor et al nor LaGrone disclose/teach:

i) the liposome to have a diameter of between 30 to 250 nanometers, and

ii) the active agent is present in the lipid-active agent complex in a ratio between 1:5 (17%) and 1:7 (12%).

However, at the time of the invention, Haas et al disclosed liposome compositions in which the therapeutic active agent is present in the liposome in an amount about 0.1mol% to about 50mol% to about 5mol% to about 10mol% based upon the liposomal components [0015]. The liposomes have a diameter of about 50 to 2000 nanometers, about 20 to 400nm, or about 50 to 300nm. [0062].

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in lipid-active agent complex formation. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to prepare lipid-active agent complexes, i.e. liposomes, to have a diameter of between 30 to 250 nanometers as per the teachings of Haas et al with a reasonable expectation of success because in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). An artisan would be motivated to prepare

lipid-active agent complexes, i.e. liposomes, to have a diameter of between 30 to 250 nanometers as per the teachings of Haas et al because the formation of lipid-active agent complexes is old technology and routine in the art, and it is routine procedure to optimize component amounts to arrive at an optimal product that is superior for its intended use, since it has been held where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. See M.P.E.P. §2144.05.

It also would have been obvious to one of ordinary skill in the art to prepare lipid-active agent complexes, i.e. liposomes, to comprise the active agent in an drug:lipid ratio of 5:1 to 7:1 as per the teachings of Haas et al with a reasonable expectation of success because in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). An artisan would be motivated to prepare lipid-active agent complexes, i.e. liposomes, to comprise the active agent in an drug:lipid ratio of 5:1 to 7:1 because such is considered routine optimization when formulating a pharmaceutical compound to achieve the desired therapeutic effect (Haas et al, [0300-0307]).

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

14. **Claims 50 and 53 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Hartmann et al (U.S. Patent 6,949,520) in view of Arigita et al (Infection and Immunity 71(9): 5210-5218, 2003), Figdor et al (U.S. Patent 7,148,329), LaGrone (U.S. Patent 5,981,493) and Haas et al (U.S. 2005/0181038), as applied to Claims 1-2, 6, 9-10, 15-16, 26-28, 37-39, 41-44, 52, 58-59 and 81 above, and in view of Charan et al (2000; *of record in specification).

Determining the scope and contents of the prior art.

Neither Hartmann et al, Arigita et al, Figdor et al, LaGrone nor Haas et al disclose/teach the plant lectin to be a Myrianthus holstii (MHL) lectin. However, at the time of the invention, Charan et al taught that MHL lectin has potent anti-HIV activity. MHL shows significant

homology with other plant lectins, such as wheat germ agglutinin, rice lectin, as well as chitinases isolated from maize and tobacco.

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in lipid-active agent complex formation. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a first plant lectin as taught by LaGrone with a second plant lectin, specifically MHL, as taught by Charan et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be

motivated to substitute a first plant lectin with a second plant lectin, specifically MHL, because Charan et al taught that MHL lectin has potent anti-HIV activity.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

15. **Claim 57 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Hartmann et al (U.S. Patent 6,949,520) in view of Arigita et al (Infection and Immunity 71(9): 5210-5218, 2003), Figdor et al (U.S. Patent 7,148,329), LaGrone (U.S. Patent 5,981,493), Haas et al (U.S. 2005/0181038) and Charan et al (2000; *of record in specification), as applied to Claims 1-2, 6, 9-10, 15-16, 26-28, 37-39, 41-44, 50, 52-53, 58-59 and 81 above, and in view of Matthiesen (WO 03/010188).

Determining the scope and contents of the prior art.

Neither Hartmann et al, Arigita et al, Figdor et al, LaGrone, Haas et al nor Charan et al disclose/teach the MHL plant lectin to be in di- or multimeric form. However, at the time of the invention, Matthiesen disclosed a means of preparing pharmaceutical lectin formulations, wherein the active form of the pharmaceutical lectin may be a dimer or multimer (Abstract, pg 12, lines 16-22).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in lipid-active agent complex formation. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple

patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a monomeric lectin as taught by LaGrone with a dimeric or multimeric form of said lectin as taught by Matthiesen with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute a monomeric lectin with a dimeric or multimeric form of a lectin because lectins are often found naturally in various low-mass forms and oligomerization allows the artisan to be in control of the mass distribution of a lectin pharmaceutical, thereby achieving greater control over the biological properties of the pharmaceutical lectin.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

16. **Claim 56 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Hartmann et al (U.S. Patent 6,949,520) in view of Arigita et al (Infection and Immunity 71(9): 5210-5218, 2003), Figdor et al (U.S. Patent 7,148,329), LaGrone (U.S. Patent 5,981,493), Haas et al (U.S. 2005/0181038) and Charan et al (2000; *of record in specification) and Matthiesen (WO

03/010188), as applied to Claims 1-2, 6, 9-10, 15-16, 26-28, 37-39, 41-44, 50, 52-53, 57-59 and 81 above, and in view of Khwaja (U.S. Patent 5,547,674).

Determining the scope and contents of the prior art.

Neither Hartmann et al, Arigita et al, Figdor et al, LaGrone, Haas et al, Charan et al nor Matthiesen disclose/teach the lipid-acti. However, at the time of the invention, Khwaja disclosed mistletoe extracts comprising lectins as an anti-HIV pharmaceutical. Some lectins are Ca2+-dependent sugar binding proteins, while others are non-Ca2+-dependent (col.'s 7-8; Table 1).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in lipid-active agent complex formation. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to try including Ca2+ and transition-metal ions in a lipid-plant lectin complex because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense."An artisan would be motivated to try including Ca2+ and transition-metal ions in a lipid-plant lectin complex because those of ordinary skill in the art have long-recognized that some

lectins are Ca2+-dependent sugar binding proteins, while others are non-Ca2+-dependent, and thus it is considered routine optimization to add Ca2+ and/or transition-metal ions to improve the ability of a lectin to bind to a desired target molecule.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

17. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/

Examiner, Art Unit 1633